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Effect of cold stimulation on myocardial perfusion
An investigation using thallium-201 scintigraphy

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SUMMARY Thallium-201 scintigraphy was used to investigate the effects of cold stimulation on myocardial perfusion in 12 patients with documented coronary artery disease (group 1), nine with chest pain but without evidence of structural coronary artery disease (group 2), and 10 normal volunteers (group 3). The scintigrams were assessed both visually and numerically using a circumferential profile technique. Transient perfusion defects were identified by both techniques in six subjects in group 1, three in group 2, and two in group 3. The haemodynamic responses (assessed by the double product) of subjects with or without transient perfusion defects were not significantly different.

Thus cold stimulation can provoke abnormalities of myocardial perfusion not only in patients with coronary heart disease but also in those with structurally normal coronary arteries and in some normal subjects. These results may reflect a spectrum of coronary vasomotor responsiveness to cold stimulation in both normal and ischaemic populations, and it is concluded that cold pressor techniques cannot be relied on to differentiate patients with coronary heart disease from those with atypical chest pain syndromes or even from normal subjects.

It has been reported that normal subjects and those with either coronary heart disease or cardiomyopathy can be differentiated on the basis of the left ventricular ejection fraction response to cold stimulation.[1] The reliability of the method has since been challenged.[2] We have also found it unsatisfactory since occasionally we have seen an abnormal[1] ejection fraction response in normal volunteers and in patients with normal coronary arteriograms. These observations and the finding of abnormal ejection fraction responses in a group of diabetics without symptoms or other clinical evidence of coronary heart disease[3] led us to question not only the value of the investigation but also the mechanisms underlying the cardiac response to cold stimulation. The aim of the present study was to use thallium scintigraphy to investigate the effect of cold stimulation on myocardial perfusion.

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Patients and methods

Thirty one subjects were investigated; all gave their informed consent. They comprised three groups. Group 1 consisted of 12 patients (nine men, three women; mean (SD) age 46 (7) years) with coronary heart disease. Four patients had electrocardiographic features of previous myocardial infarction, and one of these did not undergo coronary angiography; the remainder had angiographic evidence of significant (>50% stenosis) coronary artery disease. Group 2 consisted of nine patients (four men, five women; mean (SD) age 45 (6) years) with chest pain in whom there was no evidence of structural coronary artery disease or cardiomyopathy on angiography. Group 3 consisted of 10 normal volunteers (10 men, mean (SD) age 27 (5) years) without symptoms of clinical evidence of cardiovascular disease.

After a 10 minute rest period basal heart rate (from a single lead electrocardiogram) and cuff blood pressure were noted. The subject then immersed both hands to the wrist in a mixture of ice and water for two minutes. After the first minute, 80 MBq (2·21

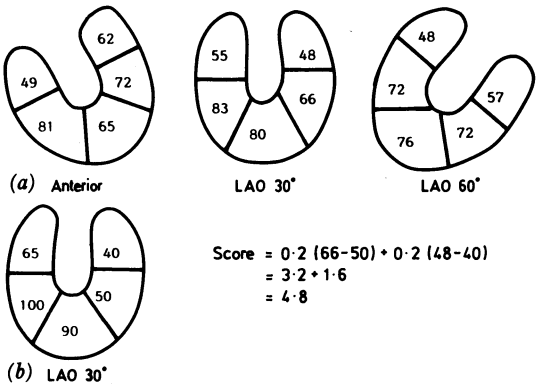

Fig. 1 *(a) Diagram showing three projections of the myocardium with the regions of interest used in the analysis indicated. The normal limits (see text) are shown. (b) Example of the scoring system for left anterior oblique (LAO) 30° projection.*

mCi) thallium-201 was injected intravenously, and at the end of the second minute the measurements of heart rate and blood pressure were repeated. Five minutes after the isotope was injected the subject was positioned under a gammacamera (Technicaire Sigma-410). After acquisition had been terminated at 400 000 counts three stress images (anterior, left anterior oblique 30°, and left anterior oblique 60°) were recorded. Corresponding redistribution images were acquired four hours later. The images were stored on magnetic tape for subsequent computer analysis (Technicaire VIP-460).

ANALYSIS

The scintigrams were analysed both visually and numerically.

Visual—The unprocessed images photographed from the video display were assessed by three observers, and a consensus was obtained. (When a defect was identified in one or more views the scintigram was classified as abnormal.) Perfusion defects were identified and defined as (*a*) stress transient (identified on stress scintigram only), (*b*) redistribution transient (identified on redistribution scintigram only), and (*c*) permanent.

Numerical—The unprocessed images were assessed by a circumferential profile technique similar to that described by Burow *et al.*[4] For each image, five regions of approximately equal area were marked on the myocardium (Fig. 1a). A larger background region

Table 1 *Change in double product (heart rate × mean blood pressure) and results of the visual and of the numerical analyses with defect score limit of >2, >1, and >0·5*

Case Nos	Change in double product (mm Hg/min)	Transient stress defect				Transient redistribution defect				Permanent defect			
		Visual	Numerical			Visual	Numerical			Visual	Numerical		
			>2	>1	>0·5		>2	>1	>0·5		>2	>1	>0·5
						Group 1							
1	2467	+	+	+	+	−	−	−	−	−	−	−	−
2	3907	+	+	+	+	−	−	−	−	−	−	−	−
3	3067	+	+	+	+	+	−	−	−	−	−	−	−
4	2406	+	+	+	+	+	−	−	−	−	−	−	−
5	1967	+	+	+	+	+	+	+	+	−	−	−	−
6	165	+	+	+	−	−	−	−	−	+	+	+	+
7	1833	+	−	−	+	−	−	−	−	+	−	−	−
8	2453	+	−	−	−	−	−	+	+	−	−	−	+
9	1740	−	+	+	+	+	+	+	+	−	−	−	−
10	643	−	−	+	+	−	−	+	+	+	+	+	+
11	3787	−	−	+	+	−	−	−	−	+	+	+	+
12	5647	−	+	−	−	−	−	−	−	+	+	+	+
						Group 2							
1	440	+	+	+	+	+	+	+	+	+	−	−	+
2	3848	+	+	+	−	−	−	−	−	−	+	+	+
3	3473	+	−	+	+	−	−	−	−	+	−	−	−
4	2820	+	−	−	−	−	−	+	+	+	+	+	+
5	1040	−	+	+	−	−	−	−	−	−	−	−	+
6	3353	−	−	−	−	−	−	−	−	−	−	−	−
7	2429	−	−	−	−	−	−	−	−	−	−	−	−
8	2728	−	−	−	−	−	−	−	−	−	−	−	−
9	6667	−	−	−	−	−	−	−	−	−	−	−	−
						*Group 3**							
1	2963	+	−	+	+	−				−			
2	3033	+	−	+	+	−				−			
3	4394	+	−	−	+	−				−			
4	3220	−	−	+	+	−				−			

*Remaining six subjects had no abnormality detected (mean change in double product 1932 (1230) mm Hg/min).
+Positive; −, negative.

Table 2 *Comparison of visual and numerical analyses of abnormal scintigrams of patients with defect score limits >2 and >1. Figures are numbers of patients*

Subject groups	*Visual*	*Numerical*		*Visual and numerical*	
		>2	*>1*	*>2*	*>1*
		Transient stress defect			
1	8	8	9	6	6
2	4	3	4	2	3
3	3	0	3	0	2
		Transient redistribution defect			
1	4	2	4	2	2
2	1	1	2	1	1
3	0	—	—	—	—
		Permanent defect			
1	5	4	4	4	4
2	3	2	2	1	1
3	0	—	—	—	—

was outlined over the lung close to the left ventricle. After background subtraction, the region with the maximum count density was established, and the count densities of the other regions were expressed as a percentage of this. The redistribution scintigrams of the 10 normal subjects were used as a standard, and the limits of normality for each region of interest were set at 2 standard deviations from the mean percentages on these images (Fig. 1a). These criteria allowed perfusion defects to be identified, and to quantify them a scoring system was used (Fig. 1b). Defect scores were calculated for all three projections. The projection was regarded as abnormal if the defect score exceeded an arbitrary limit; the three limits set (in ascending order of sensitivity) were 2, 1, and 0·5. When a perfusion defect was thus defined in one or more projections the scintigram was classified as abnormal.

Results

ANALYSIS OF SCINTIGRAMS

The scintigraphic findings are presented in detail in Table 1 and summarised in Table 2. The total numbers of perfusion defects detected visually and numerically were similar (Table 2), but the two methods produced discrepant findings in individual cases (Table 1). These discrepancies are excluded from the final results (Table 2), and only the results of abnormal scintigrams detected both visually and numerically (with defect scores >2 and >1) are given. On this basis and with the defect score limit set at 1, transient perfusion defects (Fig. 2) were detected on the stress scintigrams of six patients with coronary artery disease (group 1), of three with normal coronary arteriograms (group 2), and of two normal subjects (group 3); χ^2 analysis of these data shows no significant difference between the groups. Similarly, transient perfusion defects were detected on the redistribution scans of two patients in group 1 and of one in group 2, whereas permanent defects were detected in the four patients in group 1 with electrocardiographic evidence of myocardial infarction and in one patient in group 2.

HAEMODYNAMIC RESPONSE

The change in double product (heart rate × mean blood pressure) varied in individual cases from 165 to 6670 mm Hg/min. The mean (SD) changes in heart rate for groups 1, 2, and 3 were +3·2 (10·0), +6·3 (8·3), and +4·0 (10·6) beats/min respectively and the mean (SD) changes in double product for groups 1, 2, and 3 were 2506 (1480), 2955 (1728), and 2520 (1251) mm Hg/min respectively; the differences are not significant. The mean changes in double product for group 1 patients with and without transient stress defects were +2230 (1255) (n=6) and +2684 (1779) (n=6) respectively (NS); the corresponding values for group 2 patients were +2586 (1868) (n=3) and +3140 (1806) (n=6) respectively (NS). When the results for groups 1 and 2 are combined, there was no significant difference between the mean change in double product in patients with (2415 (1368)) and those without (+2912 (1726)) transient perfusion defects on their stress scintigrams.

Discussion

The interpretation of thallium scintigrams is known to be problematic.[4 5] The scintigrams in this study were therefore analysed both visually and numerically, and with a view to increased specificity discrepancies between the two methods (potential false positives) were excluded from the final results. The findings have, however, been given in full to show where discrepancies arose.

Permanent defects and transient redistribution defects were detected, but it is the transient stress defects that are most relevant. The scintigraphic findings in group 1 and 2 indicate that cold stimulation can provoke transient abnormalities of myocardial perfusion not only in patients with coronary heart disease but also in those in whom chest pain is not associated with structural disease of the coronary arteries. Furthermore, although in group 3 the abnormalities detected visually were only corroborated numerically when the defect score was set at 1, and the evidence is thus less strong, our findings also suggest that cold stimulation can provoke non-homogeneous myocardial perfusion in some normal subjects.

As in other studies,[1 2 6 7] the haemodynamic response to cold stimulation was small and in terms of the change in double product was much less than that

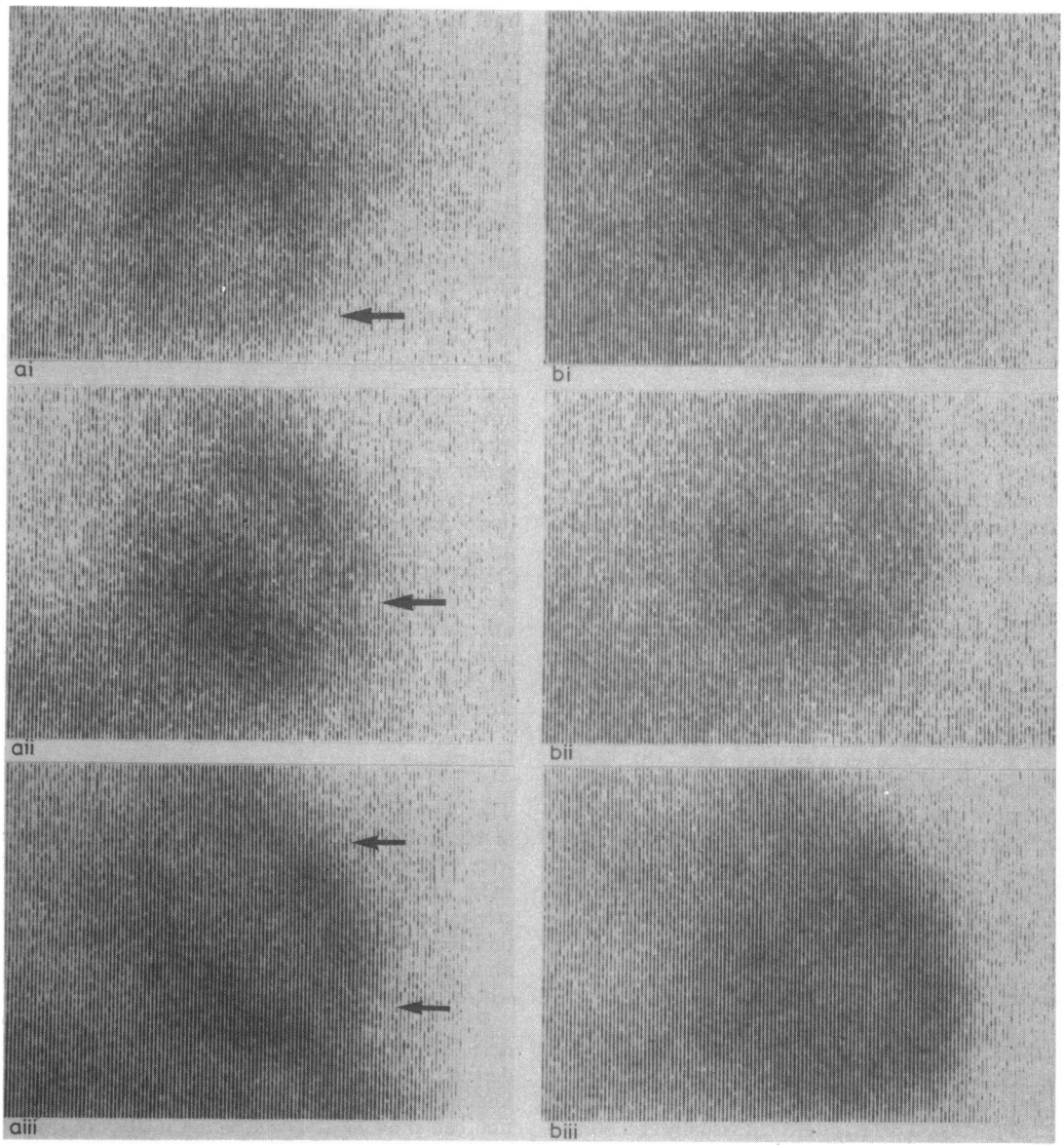

Fig. 2 *Thallium-201 scintigrams showing transient perfusion defects (arrows); (a) stress and (b) redistribution images of subjects in (i) group 1 (LAO 30°), (ii) group 2 (anterior), and (iii) group 3 (anterior).*

seen in response to dynamic or even isometric exercise.[8] The resultant increase in haemodynamic load would not be expected to be critical in patients with normal coronary arteries nor, indeed, in most patients with coronary heart disease. None the less, we did detect perfusion defects, and it is reasonable to conclude that the effect of cold stimulation on myocardial perfusion and thus on left ventricular performance is not determined solely by the haemodynamic load which it imposes. This conclusion is strengthened by the fact that there was no significant difference between the haemodynamic responses of patients with and without identifiable transient perfusion defects and in particular by the fact that transient defects were detected even when there was only a minimal change in double product (case 6, group 1, and case 1, group 2).

Left ventricular end diastolic pressure increases

with cold stimulation in patients with normal[7] and with abnormal[7 9] coronary arteriograms. Thus in theory our findings could reflect direct diastolic compression of the distal resistance vessels with a resultant reduction in coronary flow. Although this explanation cannot be discounted it should be noted that haemodynamic studies[7 9] have provided no evidence that the raised left ventricular diastolic pressure is the cause rather than the result of impaired coronary flow. Raizner *et al* made arteriographic and quantitative angiographic observations on patients presenting with chest pain.[10] They reported that cold stimulation sometimes provokes focal coronary spasm in patients with coronary heart disease and frequently provokes generalised coronary vasoconstriction in patients both with and without structural disease of the coronary arteries. Although we have no proof of spasm, our findings can be interpreted as indirect support for Raizner's observations; in addition, they suggest that cold stimulation may provoke significant coronary vasoconstriction in some normal subjects.

Our results provide a pathophysiological basis for the reduction in left ventricular ejection fraction provoked by cold stimulation in patients with coronary heart disease[1 2] and for the reductions seen in some patients with normal coronary arteriograms and in some normal subjects.[2 11] It is relevant that we have previously measured the ejection fraction response to cold stimulation in a number of the patients investigated here. The change in left ventricular ejection fraction in patients in group 1 (n=8) ranged from −8% to −33% (mean −17%) and in those in group 2 (n=6) from +25% to −21% (mean −3%); in addition, in one subject in group 3 (case 3, Table 1), there was a reduction in ejection fraction of 15%.

Whatever the precise mechanism underlying them, the practical implication of our findings is that whether its effects are assessed by thallium-201 scintigraphy or by the left ventricular ejection fraction response, cold stimulation cannot be relied on to differentiate between patients with coronary heart disease and those with structurally normal coronary arteries. Ahmad *et al* have taken a more optimistic view of the reliability of cold pressor thallium scintigraphy.[6] It should, however, be noted that they relied solely on a visual assessment of the scintigrams and that because their study group of 46 included only five patients with normal coronary arteries, they were unable to comment on the specificity of the method. While our conclusions on the diagnostic value of the ejection fraction response to cold stimulation are at variance with those of Wainwright *et al*,[1] there was in fact a degree of overlap between the normal and abnormal groups in their study; for example, five of the 28 abnormal patients had ejection fraction responses within the normal range set by the authors.

To explain both the poor diagnostic specificity of the cold pressor techniques and the high incidence of abnormalities in patients with coronary heart disease, like Raizner *et al*[10] we postulate a spectrum of coronary vasomotor responsiveness to cold stimulation in both normal and ischaemic populations. In normal subjects we suggest that the response to cold stimulation is determined by the degree of coronary vasoconstriction, which in some instances is sufficient to produce a focal abnormality of myocardial perfusion or impairment of left ventricular performance or both. We suggest that the response in patients with coronary heart disease and normal left ventricular function is determined in the same way with the important difference that in this context even minimal constriction of normal or diseased arterial segments could be expected to provoke abnormalities. In contrast, in patients with impaired left ventricular performance, and particularly in those with severe triple vessel disease, we consider that vasoconstriction is of less importance and that the induced increase in double product may be the major, and occasionally the sole, determinant of the response.

Cunningham *et al* have demonstrated an increase in peripheral vascular reactivity in young diabetic subjects.[12] We suggest that the abnormal ejection fraction responses to cold stimulation which we have observed in young diabetics[3] may reflect a similarly increased reactivity in the coronary vasculature.

The findings of this study have led us to abandon the use of cold pressor techniques in the diagnosis of coronary heart disease. They have also led us to a useful reappraisal of the clinical significance of the abnormal ejection fraction responses to cold stimulation which we have previously observed in diabetic subjects.[3]

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